Claims 1-31 are pending in the present application. Claims 1-15, 21-24 and 26-31 have been withdrawn from consideration; claim17 is canceled herein and claims 32 through 35 are added. Accordingly, claims 16, 18, 19, 20, 25 and 32-35 are presented for examination on the merits.

Claim16 and 18 have been amended to delete the recitation of "fragments, analogs and derivatives thereof." Claim 16 has further been amended to recite "95% identity" as set forth on page 24, lines 20-25. Claims 19, 20 and 25 have been amended merely to correct dependencies. Claim 25 has further been amended to include combinations of the recited polypeptides. Support for this amendment is found at the top of page 67.

New claims 32 through 35 are directed to preferred embodiments of the invention and are fully supported by original claims 16 and 25. New claims 36 and 37 are directed to peptides and vaccine compositons, respectively, that include specified peptides. These claims are supported by original claims 16 and 25.

Accordingly, no new matter is added by these amendments to the claims.

I. Objections to the Specification

It is respectfully submitted that the amendments to the specification render the formal grounds of rejection moot.

II. Rejection of Claims 16-20 Under 35 U.S.C. § 101

Claims 16-20 are rejected under 35 U.S.C. § 101 because the claimed invention allegedly is not supported by a specific, credible and substantial asserted utility or a

well-established utility. The Examiner states that the specification does not disclose that the claimed polypeptides correlate with or have a well-established utility.

Applicants respectfully disagree with the Examiner's conclusion.

The specification provides the sequence of the full length BVH-3 protein (SEQ ID NO. 2), as well as the amino acid sequence of the mature, or processed form of the polypeptide (SEQ ID NO. 55). The full-length polypeptide has a signal sequence at its N-terminus, which is lacking in the mature polypeptide. The N-terminus of SEQ ID NO. 2 contains the sequence, L-X-X-C (amino acids 18-21), which is the consensus signal peptidase cleavage site of lipoprotein modification or processing. The presence of the signal peptide is accepted in the art as evidence that the polypeptide is secreted and thus, appears on the surface of the bacterium. As such, the polypeptide is available as a marker of *Streptococcus* infection, or at the very least, a marker of the presence of contaminating bacteria in a sample.

The specification also provides evidence that the polypeptide and the claimed, specified fragments are antigenic. The polypeptide and various fragments were used to generate monoclonal antibodies that specifically bind to specified epitopes on the polypeptides of the invention. The data in Table 4 (page 56) demonstrate that antibodies specific to the claimed polypeptides can be generated and used to identify the claimed polypeptides with specificity.

The specification also provides evidence of the successful use of the claimed polypeptides to elicit an immune response that is effective to protect against challenge with two different virulent strains of *S. pneumoniae* (Example 11, Tables 6 and 7). The fact that these polypeptides were protective against two different strains of

Streptococcus that were delivered *via* two different mechanisms, i.e., intranasally and systemically, indicates that these polypeptides are indeed protective.

The specification discloses that the claimed polypeptides and fragments contain antigenic sites that induce a protective immune response when administered *in vivo*. In particular, the data in Table 8 clearly demonstrate the ability of the claimed polypeptides to elicit a protective immune response *in vivo*.

As set forth in Dr. Hamel's Declaration, enclosed herewith, data from active and protection studies using animals vaccinated with BVH-3 truncates including BVH-3B, NEW1, NEW2, NEW3 and NEW15 or antibodies reactive with the latter confirmed the protective activity of immune responses to the claimed BVH-3 gene fragments where protection was measured by either an increase in the survival rate or survival period for the vaccinated groups compared to the mock vaccinated animals.

The data are set forth in the table below.

Table 1. Protection mediated by recombinant BVH-3 truncates[a]

Immunogen	No. of mice alive : no. of mice dead 13 days post-challenge	Median day of death
BVH-3M	8 : 0	>13
NEW1	8 : 0	>13
NEW3	5 : 3	>13
BVH-15	5 : 3	>13
None	0 : 8	2

[a] Vaccinated mice were challenged intravenously with virulent pneumococci.

Protection against experimental infection was observed in mice vaccinated with BVH-3M, NEW1, NEW3 or NEW15 when compared to the mice injected with the adjuvant alone. Table 2 below illustrates the protection conferred by passive transfer of rabbit antibodies raised to BVH-3M molecule to CBA/N mice prior challenge with pneumococci.

Table 2. Protection mediated by rabbit antibodies raised to BVH-3M proteins in mice passive administered with antibody prior experimental infection with virulent S. pneumoniae WU2

Antibodies	Competitor	alive : dead[a]	Median days alive
Anti-BVH-3M	No competitor	5 : 0	>14
Anti-BVH-3M	NEW1	0 : 5	2
Anti-BVH-3M	NEW2	5 : 0	>14
Anti-BVH-3M	NEW3	5 : 0	>14
Anti-BVH-3M	NEW2 +NEW3	2 : 3	5
preimmune	No competitor	0 : 5	2
none	none	0 : 3	2

[a] The number of mice alive versus the number of mice dead on day 14 post-challenge.

The incubation of rabbit BVH-3M antibodies with soluble antigen competitors to block the antigen binding sites of the antibodies was performed in order to establish the specificity of the protective antibodies. The observation that NEW1 abolished the protection clearly indicates the specificity of protective anti-BVH-3M antibodies for NEW1 epitopes. NEW2 (residues 472-800) and NEW3 (residues 800-1039) correspond to the first (amino' end) and second half (carboxyl-end) of NEW1 molecule, respectively. Combinations of NEW2 and NEW3 were required to significantly block the protective anti-BVH-3M effect, while no effect was observed when these molecules were used individually, thus indicating that protective epitopes are present on both NEW1 subfragments, NEW2 and NEW3.

Similarly, the data in the specification show that BVH-11 truncates designated BVH-11B (also called NEW13), BVH-11C, NEW4, NEW5, NEW6, NEW8, NEW9 (*see* Example 11) and NEW16 provided protection against experimental disease and are thus useful vaccine components.

Furthermore, molecular and antigenic conservation studies revealed that the BVH-3 gene (SEQ ID NO. 1, 11) and BVH-11-2 gene (SEQ ID NO. 13) and/or protein (SEQ ID NO. 2 and SEQ ID NO. 14, respectively) were present in most, if not all of the 150 *S. pneumoniae* strains tested, independent of the capsular serotype. These observations make it clear that the claimed polypeptides and fragments thereof have universal vaccine capability to prevent infection by any *S. pneumoniae* disease.

Further, an alignment of the amino acid sequences of BVH-3 of several different strains shows that these polypeptides differ from one another at several sites (Figure 11 and Table 1 and Figure 1 of Dr. Hamel's Declaration). Applicants' studies have

provided sufficient information concerning the location of the immunogenic epitope to allow the skilled practitioner to make changes to the claimed polypeptides with a high expectation of successfully retaining immunogenicity (*See* enclosed figure of epitope localization of the BHV-3 peptide). It follows therefore, that the claimed polypeptides can tolerate at least 5 % amino acid sequence divergence, and still elicit an immune response.

Thus, there is sufficient disclosure in the specification of a specific, substantial and credible utility of the claimed polypeptides. Accordingly, the rejection of claims 16-20 under 35 U.S.C. § 101 is respectfully traversed.

III. Rejection of Claims 16-20 and 25 under 35 U.S.C. § 112, First Paragraph

The Examiner states that one of ordinary skill in the art would not know how to use the claimed invention because the specification does not support a credible utility.

This rejection is respectfully traversed as follows.

Applicants' evidence and arguments regarding the utility of the claimed invention as set forth above are incorporated herein. It is respectfully submitted that the skilled practitioner can make and use the claimed invention by following the guidelines set forth in the specification. The specification teaches the cloning of specific polypeptides, demonstrates their antigenicity and ability to elicit a protective immune response, and teaches the location of epitopes that give rise to a protective response. Thus, the specification clearly provides sufficient guidance to the skilled practitioner to make and use the claimed polypeptides and vaccine.

Accordingly, the rejection of claims 16-20 and 25 under 35 U.S.C. § 112, first paragraph, is respectfully traversed.

IV. Rejection of Claims 16-20 and 25 under 35 U.S.C. § 112, Second Paragraph

It is respectfully submitted that the amendments to the claims render the formal grounds of rejection moot.

V. Rejection of Claims 16-20 and 25 Under 35 U.S.C. § 112, First Paragraph

The Examiner states that the description of SEQ ID NO. 2 and the other specific sequences for BVH-3 polypeptide meet the written description and enablement requirements of 35 U.S.C. § 112. However, the Examiner asserts that the skilled practitioner cannot envision the detailed chemical structure of the encompassed polypeptides.

This rejection is respectfully traversed as follows.

The present claims are directed to polypeptides having a specified amino acid sequence or polypeptides that differ therefrom by 5 % or less. As can be seen from Figure 11 of the specification and the data presented in Dr. Hamel's Declaration (Figure 1 and Table 1), at least that amount of difference occurs in nature.

Moreover, the specification discloses at least one large region of SEQ ID NO. 2, which contains epitopes that confer protective immunity. Thus, one of skill in the art would recognize that amino acid changes might be safely made outside that region. The specification also teaches that conservative amino acid changes may be made to retain antigenicity.

On the basis of the present disclosure the skilled practitioner can envision polypeptides having 5% amino acid changes or fewer relative to the sequences disclosed in the specification. That these slightly altered sequences will confer immunity to or serve as specific markers of *Streptococcus* is evidenced by the ability of the claimed polypeptides to confer immunity to a broad range of *Streptococcus* serotypes. Further evidence that these slightly altered polypeptides work is the fact that such polypeptides exist in nature (Figure 11 and Table 1 and Figure 1 of Dr. Hamel's Declaration). Thus, the genus encompassed by the present claims is fully supported by the specification.

Accordingly, the rejection of claims 16-20 and 25 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

VI. Rejection of Claims 16-20 and 25 Under 35 U.S.C. § 112, First Paragraph

Claims 16-20 and 25 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide an enabling disclosure commensurate in scope with the claims.

This rejection is respectfully traversed as follows.

The present claims are directed to polypeptides having specified amino acid sequences and polypeptides that differ from those polypeptides by 5 % or less. The specification provides examples of the successful use of a subset of the claimed polypeptides to elicit a protective immune response against *S. pneumoniae.* Example 11 (pages 59-64) discloses the use of a subset of the claimed polypeptides to immunize mice against two of the most virulent strains of *S. pneumoniae*, WU2 and P4142. The

results are reported in Tables 6 and 7 of the specification. As can be seen, mice were protected against infection by the polypeptides of the invention.

The Examiner also stated that the specification provides an enabling disclosure of use of the polypeptide of SEQ ID NO.2 for the induction of an immune response when combined with QuilA. It appears that the Examiner is trying to limit the invention to the examples in the disclosure. However, "[a]s the Federal Circuit instructs, that a claim may be broader than any specific example disclosed in the patent is of no moment." *Ralston Purina Co. v. Far-Mor-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985), citing *In re Rasmussen*, 650 F.2d 1212, 1215 (CCPA 1981).

QuilA is merely one example of an adjuvant known to work in mice and can readily be replaced by another adjuvant, for example an adjuvant known to work in humans, such as alum, cholera toxin or cytokines, or Freund's adjuvant in animals. Adjuvants are well known in the art and their use and selection is routine. Thus, the specification provides an enabling disclosure of the claimed polypeptides with any adjuvant, carrier or diluent.

It is respectfully submitted that the specification is enabling for the full scope of the present claims. Accordingly, the rejection of claims 16-20 and 25 is respectfully traversed.

VII. Rejection of Claims 16-20 and 25 Under 35 U.S.C. § 102(a)

Claims 16-20 and 25 are rejected under 35 U.S.C. § 102(a) over WO98/18930, which discloses a partial amino acid sequence of the mature BVH-3 polypeptide, and two additional amino acid sequences that share 78.6% sequence

similarity to SEQ ID NO. 2 over 103 amino acids. The Examiner concludes, therefore, that the claimed invention is inherently anticipated by the cited reference.

This rejection is respectfully traversed as follows.

The present invention is directed to polypeptides having specified amino acid sequences or having at least 95% sequence similarity to the specified sequences. The claimed polypeptides are thus, not anticipated by the disclosure of a different fragment of BVH-3 than claimed or amino acid sequences sharing less than 95% sequence identity with the claimed polypeptides.

Moreover, the prior art fragment falls within the region of the BVH-3 polypeptide shown by Applicants to lack immunity inducing capability. Thus, the prior art fragment neither anticipates, nor renders obvious present claims 25 or 33-37, which are directed to vaccines, which encompass polypeptides shown herein to confer protective immunity.

Accordingly, the rejection of claims 16-20 under 35 U.S.C. § 102(a) over the Human Genome Science disclosure of SEQ ID NO.182, 56 and 66.

It is respectfully submitted that the present application is in condition for allowance, an early notification thereof being earnestly solicited. If any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned attorney so that prosecution of this application may be expedited.

To the extent necessary, please charge any shortage in fees due, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such account.

Respectfully submitted,

McDERMOTT, WILL & EMERY

Date: _____ By: _____

Judith L. Toffenetti
Registration No. 39,048

600 13th Street, N.W. , Suite 1200
Washington, D.C. 20006-3096
Telephone: (202) 756-8000
Facsimile: (202) 756-8087

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please substitute the following sentence for the first sentence following the title on page 1 of the specification:

--This application claims priority from US patent application 60/113,800, filed [december] December 23, 1998, which is herein incorporated by reference.--

Please replace the first full paragraph on page 2 with the following paragraph:

--PCT publication number WO98/18930 published [may] May 7, 1998, entitled "Streptococcus [Pneumoniae] *pneumoniae* antigens and vaccines" describes certain polypeptides which are claimed to be antigenic. However, no biological activity of these polypeptides is reported.--

Please replace the first full paragraph on page 35 with the following paragraph:

--The DNA probes of this invention may also be used for detecting circulating streptococcus, i.e., [*S. pneumoniae*nucleic acids] *S. pneumoniae* nucleic acids in a sample, for example using a polymerase chain reaction, as a method of diagnosing streptococcus infections. The probe may be synthesized using conventional techniques and may be immobilized on a solid phase, or may be labeled with a detectable label. A preferred DNA probe for this application is an oligomer having a sequence complementary to at least 6 contiguous nucleotides of the [streptococcus pneumoniae] *Streptococcus pneumoniae* of the invention.--

IN THE CLAIMS:

Please cancel claim 17 in its entirety and without prejudice.

Please amend claims 16, 18-20 and 25 and add new claims 32 to 37 as follows:

Claim 16 (Amended). An isolated polypeptide having at least [70] 95 % identity [to] with a second polypeptide having an amino acid sequence [chosen from:] of any one of SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81 or 83 [or fragments, analogs or derivatives thereof].

Claim 18 (Amended). An isolated polypeptide having an amino acid sequence [chosen from] of any one of SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81 or 83 [or fragments, analogs or derivatives thereof].

Claim 19 (Amended). An isolated polypeptide according to claim 18, wherein the N-terminal [Met] methionine residue of the polypeptide is deleted.

Claim 20 (Amended). An isolated polypeptide according to claim 18, wherein the secretory amino acid sequence of the polypeptide is deleted.

Claim 25 (Amended). A vaccine composition comprising a polypeptide [according to any one of claims 16 to 24] having at least 95% identity with a second polypeptide having an amino acid sequence of any one of SEQ ID NOs: 2, 4, 6, 10, 14, 16, 55, 58, 60, 62 to 69, 71 to 75, 77 to 79, 81 or 83, or a combination thereof and a pharmaceutically acceptable carrier, diluent or adjuvant.

Please add the following claims:

Claim 32. (New) An isolated polypeptide having an amino acid sequence of SEQ ID NOs: 2, 10, 55, 58, 64, 65 or 66.

Claim 33. (New) A vaccine composition comprising a polypeptide having an amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 10, SEQ ID NO:14, SEQ ID NO: 16, SEQ ID NO: 55, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO:65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO:77, SEQ ID NO:78, and SEQ ID NO: 79 .

Claim 34. (New) A vaccine composition according to claim 25 wherein the polypeptide lacks an N-terminal methionine residue.

Claim 35. (New) A vaccine composition according to claim 25 wherein the polypeptide lacks a secretory amino acid sequence.

Claim 36. (New) An isolated polypeptide having at least 95 % identity with a second polypeptide comprising an amino acid sequence of any one of SEQ ID NOs.10, 58, 64, 65 and 66.

Claim 37. (New) A vaccine composition comprising a having at least 95% identity with a second polypeptide having an amino acid sequence of any one of SEQ ID NOs, 10, 58, 64, 65 and 66 or a combination thereof_ and a pharmaceutically acceptable carrier, diluent or adjuvant.